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(54) Title: SATIETY INDUCING COMPOSITION

(57) Abstract: The invention provides the use of a whey protein and/or whey protein hydrolysate which stimulate the cellular release of the satiety peptides cholecystokinin and glucagon-like-peptide in the preparation of edible compositions. The edible compositions can be used to control body weight and have beneficial effects on satiety. Edible compositions are also provided.

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compounds that stimulate the release of certain peptides associated with signaling, or causing, the feeling of satiety. These peptides are referred herein as "satiety peptides". Such satiety peptides include, for example, cholecystokinin (CCK), enterostatin, somatostatin, amylin and glucagon-like-peptides (GLP), such as glucagon-like-peptide-1 (GLP-1).

Although a great number of molecules or compositions have been suggested to be active in stimulating the release of one of the aforementioned satiety peptides, only very few of them have been derived from natural products and/or can be used in food products.

US 6,207,638 discloses a nutritional composition stimulating the release of CCK, the composition comprising a) a protein selected from casein, whey and soy, b) a glycomacropeptide, c) a long chain fatty acid, and d) soluble and insoluble fibers. Whey protein hydrolysates are not disclosed and no teaching is given of the release of both CCK and glucagon-like-peptides by the whey protein.

WO 01/37850 discloses a milk protein hydrolysate inducing the release of glucagon-like-peptide 1 (GLP-1). Caseino-glycomacropeptide has not been found to stimulate the cellular release of CCK.

WO 02/15719 discloses nutritional compositions comprising hydrolysed whey proteins to provide reduced satiety effects from the compositions. The nutritional compositions are intended for people suffering from reduced appetite such as those convalescing and anorexia suffers.

Powders to produce drinks comprising β-lactoglobulin and α-lactalbumin, and such drinks, are known for blood pressure lowering applications. A powder produced by Davisco Foods International (Minnesota, USA) comprises 20g of β-lactoglobulin and α-lactalbumin, 1g of fat and 6g of carbohydrate per 30g of powdered product. The powders can be mixed with water or milk to produce the drink. No disclosure is made of use in satiety control applications. The powders and drinks provide over 55% of the total calories in the powder or drink (when made with water or cow's milk) from the protein content.

However, despite the above developments, there is still a need in the art for edible compositions which provide a good satiety effect for consumers, especially those wishing to control their calorie intake and/or body weight. Furthermore, there is a need to provide such products which help with the adherence to a dietary programme, especially a calorie controlled diet or with otherwise controlling calorie intake. There is also a need for edible compositions which can be used to help improve or control perception of body image or body weight.

In particular, there is a need for edible compositions which provide an improved satiety effect compared to conventional food products or conventional diet/meal replacement products. There is also a need to provide edible compositions which have an acceptable taste as well as providing good satiety effects, e.g. the products are not too sweet, nor, too bitter.

In particular, there is a need for meal replacement products which provide one or more of the above effects and/or advantages.

An enhanced feeling of satiety as referred to herein means a more pronounced and/or quicker feeling of satiety (satiation) and/or a longer lasting feeling of satiety after eating (satiety). Such effects typically extend the time elapsed between meals and can result in a smaller amount of food and/or number of calories being consumed daily etc. The references herein to satiety include both what is strictly referred to as "satiation" and "satiety", including "end-of-meal" satiety and "between-meals" satiety.

It is believed that the cellular release of CCK in the body is associated with the feeling of satiety that occurs at the end of a meal (end-of-meal satiety) whereas the cellular release of GLP is associated with the feeling of satiety that lasts after eating (between-meals satiety). Thus, CCK release is believed to be involved in signaling to the body when a person has eaten enough of a meal and GLP is believed to be involved in signaling to the body that we are still satiated from a previous meal.

It has also been found that the WP and WPH of the present invention exhibit an increased level of induced cellular GLP release at a given concentration than do other milk proteins, milk protein hydrolysates or non-hydrolysated whey proteins.

According to a first aspect, the present invention provides the use of a whey protein and/or whey protein hydrolysate in an edible composition, the whey protein and/or whey protein hydrolysate being able to induce the cellular release of glucagon-like-peptides and cholecystokinins, wherein the whey protein and/or whey protein hydrolysate on or after consumption of the edible composition induces an enhanced feeling of satiety.

intake and/or helping adherence to a dietary plan, the method comprising the step of administering to a human or animal by means of an edible composition, an effective amount of a whey protein and/or whey protein hydrolysate which is capable of inducing the cellular release of glucagon-like peptides and cholecystokinins.

According to a further aspect, the present invention provides a liquid or flowable edible composition comprising protein, wherein the protein comprises 0.1 to 50% by weight based on the weight of the composition of a whey protein hydrolysate capable of inducing the cellular release glucagon-like-peptides and cholecystokinins, and wherein 50% or less of the total calories in the edible composition are provided by the protein.

A "flowable" product as referred to herein is a liquid, semi-liquid, powdered or particulate product which when poured with or without the application of pressure flows out of a container even if the product does not flow out in a continuous stream. The term does not include products which are in one piece (e.g. have a shaped solid form such as blocks, cubes etc) as these are not capable of flowing, nor, products which are eaten in a physical state which does not flow such as ice-cream.

The liquid or flowable edible compositions of the invention give good satiety effects, acceptable sensory properties (such as acceptable taste) and have a good balance of the level of whey protein and/or whey protein hydrolysate used and the percentage of calories in the product obtained from the total amount of protein in the composition. This combination is especially suitable for a meal replacement product.

body weight and/or body perception. There are also longer term advantages associated with helping in the prevention of diseases related to being overweight.

Except in the operating and comparative examples, or where otherwise explicitly indicated, all numbers in this description indicating amounts of material or conditions of reaction, physical properties of materials and/or use are to be understood as modified by the word "about". All amounts are as percentages by weight unless otherwise stated. For the edible compositions, all percentages are by weight based on the total weight of the composition unless otherwise stated.

The term "comprising" is meant not to be limiting to any subsequently stated elements but rather to encompass non-specified elements of major or minor functional importance. In other words the listed steps, elements or options need not be exhaustive. Whenever the words "including" or "having" are used, these terms are meant to be equivalent to "comprising" as defined above.

DETAILED DESCRIPTION

Satiety peptides

Cholecystokinin(s) and "CCK" as used herein include all peptides of the CCK family, including (but not limited to); CCK-4, CCK-8, CCK-22, CCK-23, CCK-24, CCH-25, CCK-36, CCK-27, CCK-28, CCK-29, CCK-30, CCK-31, CCK-32, CCK-33, CCK-39, CCK-58.

Glucagon-like-peptides (GLP) and "GLP" as used herein include all peptides of the GLP family including (but not limited to); GLP-1 and GLP-2. GLP-1 has been found to be especially of interest.

cellular release of CCK and GLP in the body is stimulated resulting in the satiety effect.

This cellular release can also be measured *in vivo*, for example, by measuring the increase or appearance of CCK and GLP levels in the blood of that subject after consumption of the WP and/or WPH or an edible composition comprising it. Suitable techniques for measuring the CCK and GLP levels in the blood are well known in the art and do not need to be further described here.

The WP and/or WPH of the invention show cellular release of CCK and GLP-1 in the *in vitro* cellular release test of examples 1 and 2, particularly, when used at a concentration of at least 5mg/ml.

Without wishing to be bound by theory, it is believed that the WP/WPH of the invention may provide enhanced satiety effects by at least one of the following mechanisms:

1) by triggering the release of CCK from the duodenal and jejunum mucosal (I) cells and by triggering the release of GLP-1 from mucosal L cells in the distal ileum and colon from processing of major proglucagon fragment by prohormone convertase PCI/3.
2) CCK-like peptides in the WP/WPH may activate CCK-A receptors on the gastric pylorus causing contraction resulting in gastric distension. Stomach distension activates receptors on the afferent gastric vagus nerve, which then transmits signals via the nucleus tractus solitarius (NTS) to the satiety centre of the hypothalamus.
3) CCK-like peptides in the WP/WPH may bind to receptors present in the area postema adjacent to the NTS at the base of the fourth ventricle. The blood brain barrier overlying

It is especially preferred that the WPH comprises hydrolysates of β-lactoglobulin or α-lactalbumin, most preferably mixtures thereof. The weight ratio of the β-lactoglobulin or α-lactalbumin hydrolysates in the mixture is preferably in the range of from 5:1 to 1:5, more preferably 4:1 to 1:4, such as 3.5:1 to 1:2.

One particular WPH which may be used comprises from 5 to 20% by weight of aspartic acid, 10 to 25% by weight of leucine, 5 to 20% by weight of lysine and 10 to 32 % by weight of glutamic acids.

The WPH may have a degree of hydrolysis in the range of up to 20%, preferably of from 1 to 15%, more preferably of from 2 to 10%, such as 5 to 9%. The degree of hydrolysis is determined by OPA methodology (Lee KS, Drescher DG., Fluorometric amino-acid analysis with o-phthaldialdehyde (OPA), Int. J. Biochem. 1978; 9(7): 457-467).

The WP and WPH preferably have a weight average molecular weight in the range of from about 1000 Dalton to 12000 Dalton, preferably of from 2000 Dalton to 8000 Dalton. It is preferred that 4 to 40% by weight, more preferably 10 to 30% of the WPH has a weight average molecular weight in the rage of from 2000 to 5000 Daltons and/or 1 to 30% by weight, more preferably 2 to 20 % of the WPH has a weight average molecular weight in the range of from 5000 to 10000 Daltons.

The WP and WPH preferably have a pH in the range of from 6 to 9 at 20°C in a 10 mg/ml solution in de-ionised water, more preferably of from 6.5 to 8.

administering to a human or animal an effective amount of the WP and/or WPH of the invention.

The total effective amount of WP and/or WPH administered according to the method may vary according to the needs of the person to whom it is administered. Typically total amounts of from 0.1g to 150g will be administered, preferably 1g to 80g, more preferably 5g to 50g per day. The effective daily amount may be administered by a single dose or by multiple doses.

The WP and/or WPH may be administered to the animal or human in any suitable form, for example as a capsule, tablet, solution, or, preferably as part of an edible composition as described herein including bar products and liquid products such as ready-to-drink products.

The Edible Composition

The edible composition may be in the form of a nutritional composition or supplement (such as a tablet, powder, capsule or liquid product), a food composition (product) such as a meal replacement product or a beverage.

A nutritional composition or supplement as used herein refers to a composition or supplement which provides at least one biologically beneficial agent such as vitamins, minerals, trace elements, the WPH etc and which is intended to supplement the amount of such agents obtained through normal dietary intake.

A food composition according to the invention may be any food which can be formulated to comprise the WP and/or WPH and which also contains at least one of protein, fat, and/or carbohydrate. It is preferred that the food composition is one intended to be used in a weight loss or weight control plan.

convenient form. It is especially preferred that the meal replacement product is a ready to drink liquid, a liquid produced from a soluble powdered product, a soup, a dessert, a bar, a cereal based or pasta based or noodle based product, or, a soluble or dispersible powdered product.

The edible composition may be for example; a solid product, a powdered product, a tablet, a capsule, a liquid, a flowable, spoonable, pourable or spreadable product or a bar etc. The edible composition may be a powder which is mixed with a liquid, such as water or milk, to produce a liquid or slurry product (such as a meal replacement product).

The edible compositions comprise a total amount of from 0.1% to 80% by weight of the WP and/or WPH based on the weight of the composition, preferably 0.1 to 40 or 50 %wt, more preferably 0.5 or 1 to 30%wt, most preferably 2 or 5 to 20%wt. The edible compositions preferably comprise an amount of from 0.1 to 80% by weight, preferably 1 to 50%, of hydrolysates of β-lactoglobulin, α-lactalbumin or mixtures thereof based on the weight of the composition.

According to one embodiment of the invention, the edible compositions may comprise less than 20 g in total per serving, or per product where the product is used as a single serving, of the WP and/or WPH whether or not the above-mentioned amounts are used.

If the edible composition is a liquid or flowable composition, such as liquid meal replacement product or a soup, then the total amount of WP and/or WPH will preferably be in the range of from 0.1 to 40 or 50% by weight, more preferably 0.5 or 1 to 30%wt, most preferably 2 to 20%wt based on the total weight of the composition.

The edible composition will typically comprise protein in addition to the WP and/or WPH. The total amount of protein in the composition is preferably an amount of from 0.1 to 30 or 40% by weight of the edible composition. It is preferred that the compositions comprise 0.5 to 25%wt of total protein, preferably 1 to 20 %wt. In the liquid or flowable compositions the protein present provides up to 50% of the total calories of the edible composition, more preferably between 20 % and 50%, most preferably between 25% and 50%. For the other types of edible compositions, these amounts are preferred but are not essential.

The edible composition may comprise edible fats, preferably in an amount of up to 60 or 70% by weight based on the weight of the composition, more preferably from 0.5 to 30 or 35%wt, most preferably from 0.75 to 10 or 20% fat. Any suitable fat may be used with vegetable fats being especially preferred for example, vegetable fats, plant oils, nut oils, seed oils, or mixtures thereof. Saturated or unsaturated (mono-unsaturated and poly-unsaturated) fats may be used.

The edible compositions may also comprise one or more carbohydrates, preferably in an amount of from 1 to 95% by weight based on the weight of the composition, more preferably 5 to 70%wt, most preferably 10 to 60%wt, such as 15 to 50%wt. Any suitable carbohydrate may be used, for example sucrose, lactose, glucose, fructose, corn syrup, maltodextrins, starch, modified starch or mixtures thereof.

The edible composition may also comprise dietary fibres, for example in an amount of from 0.1 to 40 or 50% by weight based on the weight of the composition, preferably 0.5 to 20%wt.

The edible composition may also comprise 0.1 to 15% by weight of edible salts based on the weight of the composition, preferably 3 to 8%wt. Any edible salts may be used, for example, sodium chloride, potassium chloride, alkali metal or alkaline earth metal salts of citric acid, lactic acid, benzoic acid, ascorbic acid, or, mixtures thereof. Calcium salts may also be used such as calcium chloride and calcium caseinate.

The edible composition may comprise one or more cholesterol lowering agents in conventional amounts. Any suitable, known, cholesterol lowering agent may be used, for example isoflavones, phytosterols, soy bean extracts, fish oil extracts, tea leaf extracts.

The edible composition may comprise up to 10 or 20% by weight, based on the weight of the composition, of minor ingredients selected from added vitamins, added minerals, herbs, spices, flavourings, aromas, antioxidants, colourants, preservatives or mixtures thereof. Preferably the compositions comprise of from 0.5 to 15% by weight, more preferably 2 to 10% of these ingredients. It is especially preferred that the compositions comprise added vitamins and minerals. These may be added by the use of vitamin premixes, mineral premixes and mixtures thereof. Alternatively the vitamins and/or minerals may be added individually. These added vitamins and/or minerals are preferably selected from at least one of vitamins A, B1, B2, B3, B5, B6, B12, biotin, C, D, E, H, K and calcium, magnesium, potassium, zinc and iron. Iodine, manganese, molybdenum, phosphorus, selenium and chromium may also be included.

The amounts of protein, fat, carbohydrate and other ingredients in the edible composition will vary according to the product

trace elements. Fibres, although not absorbed by the body, are considered herein as nutrients. Water, although it provides a benefit to the body, is not considered as a nutrient.

The consumption of a composition comprising the WP and/or WPH according to the invention may occur as a part of a dietary plan, such as those intended to reduce or control body weight. For example, a subject following that plan may be better able to reduce, control or maintain their body weight, e.g. by following the dietary plan for a longer period of time and/or adhering more closely to the plan as they feel less temptation to snack or over-eat. The term "dietary plan" as used herein includes those for controlling body weight and those followed for medical reasons.

Another advantage of the present invention is that it provides methods and compositions to treat obesity or alter gastric transit and nutrient uptake in the body, which compositions can be simply eaten rather than needing to be injected as occurs with some hormones used in the treatment of obesity.

The invention is further described by way of the following examples which are to be understood as not limiting. Further examples within the scope of the invention will be apparent to the person skilled in the art.

EXAMPLES

Examples 1 and 2: Stimulated release of GLP 1 and CCK in cultured GLUTag cells

1. Materials

a) Whey Protein Hydrolysate:

cells/well) and the plates were stored under the same incubation conditions as described above. After 3 days storage the cells were washed twice with DMEM containing 0.5% (vol/vol) FBS and then, to four series (A to D) of 3 wells, different amounts of Biozate 1 were added as detailed below. Thus, each series was prepared in triplicate. A control sample which did not have any added Biozate 1 was also prepared in triplicate.

Series A - 0.5 mg/ml Biozate 1
Series B - 3 mg/ml Biozate 1
Series C - 5 mg/ml Biozate 1
Series D - 10 mg/ml Biozate 1

The plates were incubated as detailed above and after incubation for 1 hour an aliquot was taken from each plate to measure CCK release. A further aliquot was taken from each plate after 2 hours incubation to measure GLP-1 release. The aliquots were treated as detailed below before being tested to determine CCK or GLP-1 release.

The aliquots were collected and 50μg/ml phenylmethanesulfonyl fluoride (PMSF) was added thereto. The aliquots were frozen at -80°C for subsequent analysis for CCK and GLP-1 secretion. The aliquots were defrosted and centrifuged (5000g) to remove cell debris. The CCK and GLP-1 release from the GLUTaq cells was then tested.

CCK release was measured using a commercial enzyme immunoassay kit (from Phoenix Pharmaceuticals, Belmont, California, USA) which measures CCK 26-33 non-sulfated and sulfated. According to the test kit specifications, the intra-assay variation is <5% and the inter-assay variation is <14%.

EXAMPLE 3 - meal replacement bar product

A meal replacement bar product comprising WPH may be prepared according to the formulation below.

Ingredient	Percentage by weight
Honey	16.0
Sucrose	10.0
Biozate 1 (WPH)	13.0
Whey protein*1	13.0
Chopped dried fruit and nuts	10.0
Soy flour	5.0
Peanut butter	5.0
Maltodextrin	4.0
Oats	6.0
Bran fibre	2.0
Flavourings	2.0
Vitamin / mineral premix	2.0
Chocolate flavoured coating	to 100 %wt

*1 not according to the present invention.

The bar is made by thoroughly mixing together the honey and maltodextrin with the peanut butter. The remaining ingredients except the chocolate flavoured coating are added and the mixture is further mixed and formed into a bar shape. To coat it the bar is passed through a curtain of molten chocolate flavoured coating. The bar is allowed to cool to solidify the coating.

The edible composition shows good satiety effects compared to the equivalent composition wherein the whey protein hydrolysate is replaced by the same amount of cow's milk protein.

Ingredient	Percentage by weight
Maltodextrin	39.4
Tea powder	9.0
Aspartame	2.5
Peach flavour	3.6
N&A apricot flavour	1.2
Citric acid	9.0
Magnesium oxide	0.2
Biozate 1	10.0
Vitamin premix	0.3
Calcium lactate	23.2
Water	to 100 %wt

The product shows good satiety effects (may be consumed as a diluted product) compared to the equivalent composition wherein the whey protein hydrolysate is replaced by the same amount of cow's milk protein.

In examples 3 to 5 the whey protein hydrolysate may be replaced by the non-hydrolysed whey protein according to the present invention.

amount of from 0.1% to 80% by weight based on the weight of the composition.

7. The use according to any one of the preceding claims, wherein the edible composition is a food composition used in a weight loss or weight control plan.

8. The use according to any one of the preceding claims, wherein the edible composition meal replacement product.

9. The use according to claim 8, wherein the meal replacement product is a ready-to-drink liquid, a liquid produced from a soluble powdered product, a soup, a dessert, a bar, a cereal based or pasta based or noodle based product, or, a soluble powdered product.

10. The use according to any one of the preceding claims where the composition is a liquid or flowable edible composition comprising 0.1 to 50% by weight based on the weight of the composition of said whey protein hydrolysate and wherein 50% or less of the total calories in the edible composition are provided by the protein.

11. The use according to any one claims 1 to 9 where the composition is liquid or flowable edible composition comprising 0.1 to 80% by weight based on the weight of the composition of said whey protein hydrolysate and wherein the composition further comprises added vitamins and/or minerals selected from at least one of vitamins A, B1, B2, B3, B5, B6, B11, B12, biotin, C, D, E, H, and K and calcium, magnesium, potassium, zinc and iron.

inducing the cellular release of glucagon-like peptides and cholecystokinins.

18. The method according to either one of claims 16 or 17, wherein the edible composition comprises a total amount of from 0.1% to 80% by weight based on the weight of the composition of the whey protein hydrolysate.

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(54) Title: SATIETY INDUCING COMPOSITION

(57) Abstract: The invention provides the use of a whey protein and/or whey protein hydrolysate which stimulate the cellular release of the satiety peptides cholecystokinin and glucagon-like-peptide in the preparation of edible compositions. The edible compositions can be used to control body weight and have beneficial effects on satiety. Edible compositions are also provided.

WO 2004/002241 A1

compounds that stimulate the release of certain peptides associated with signaling, or causing, the feeling of satiety. These peptides are referred herein as "satiety peptides". Such satiety peptides include, for example, cholecystokinin (CCK), enterostatin, somatostatin, amylin and glucagon-like-peptides (GLP), such as glucagon-like-peptide-1 (GLP-1).

Although a great number of molecules or compositions have been suggested to be active in stimulating the release of one of the aforementioned satiety peptides, only very few of them have been derived from natural products and/or can be used in food products.

US 6,207,638 discloses a nutritional composition stimulating the release of CCK, the composition comprising a) a protein selected from casein, whey and soy, b) a glycomacropeptide, c) a long chain fatty acid, and d) soluble and insoluble fibers. Whey protein hydrolysates are not disclosed and no teaching is given of the release of both CCK and glucagon-like-peptides by the whey protein.

WO 01/37850 discloses a milk protein hydrolysate inducing the release of glucagon-like-peptide 1 (GLP-1). Caseino-glycomacropeptide has not been found to stimulate the cellular release of CCK.

WO 02/15719 discloses nutritional compositions comprising hydrolysed whey proteins to provide reduced satiety effects from the compositions. The nutritional compositions are intended for people suffering from reduced appetite such as those convalescing and anorexia suffers.

Powders to produce drinks comprising β-lactoglobulin and α-lactalbumin, and such drinks, are known for blood pressure lowering applications. A powder produced by Davisco Foods International (Minnesota, USA) comprises 20g of β-lactoglobulin and α-lactalbumin, 1g of fat and 6g of carbohydrate per 30g of powdered product. The powders can be mixed with water or milk to produce the drink. No disclosure is made of use in satiety control applications. The powders and drinks provide over 55% of the total calories in the powder or drink (when made with water or cow's milk) from the protein content.

However, despite the above developments, there is still a need in the art for edible compositions which provide a good satiety effect for consumers, especially those wishing to control their calorie intake and/or body weight. Furthermore, there is a need to provide such products which help with the adherence to a dietary programme, especially a calorie controlled diet or with otherwise controlling calorie intake. There is also a need for edible compositions which can be used to help improve or control perception of body image or body weight.

In particular, there is a need for edible compositions which provide an improved satiety effect compared to conventional food products or conventional diet/meal replacement products. There is also a need to provide edible compositions which have an acceptable taste as well as providing good satiety effects, e.g. the products are not too sweet, nor, too bitter.

In particular, there is a need for meal replacement products which provide one or more of the above effects and/or advantages.

An enhanced feeling of satiety as referred to herein means a more pronounced and/or quicker feeling of satiety (satiation) and/or a longer lasting feeling of satiety after eating (satiety). Such effects typically extend the time elapsed between meals and can result in a smaller amount of food and/or number of calories being consumed daily etc. The references herein to satiety include both what is strictly referred to as "satiation" and "satiety", including "end-of-meal" satiety and "between-meals" satiety.

It is believed that the cellular release of CCK in the body is associated with the feeling of satiety that occurs at the end of a meal (end-of-meal satiety) whereas the cellular release of GLP is associated with the feeling of satiety that lasts after eating (between-meals satiety). Thus, CCK release is believed to be involved in signaling to the body when a person has eaten enough of a meal and GLP is believed to be involved in signaling to the body that we are still satiated from a previous meal.

It has also been found that the WP and WPH of the present invention exhibit an increased level of induced cellular GLP release at a given concentration than do other milk proteins, milk protein hydrolysates or non-hydrolysated whey proteins.

According to a first aspect, the present invention provides the use of a whey protein and/or whey protein hydrolysate in an edible composition, the whey protein and/or whey protein hydrolysate being able to induce the cellular release of glucagon-like-peptides and cholecystokinins, wherein the whey protein and/or whey protein hydrolysate on or after consumption of the edible composition induces an enhanced feeling of satiety.

intake and/or helping adherence to a dietary plan, the method comprising the step of administering to a human or animal by means of an edible composition, an effective amount of a whey protein and/or whey protein hydrolysate which is capable of inducing the cellular release of glucagon-like peptides and cholecystokinins.

According to a further aspect, the present invention provides a liquid or flowable edible composition comprising protein, wherein the protein comprises 0.1 to 50% by weight based on the weight of the composition of a whey protein hydrolysate capable of inducing the cellular release glucagon-like-peptides and cholecystokinins, and wherein 50% or less of the total calories in the edible composition are provided by the protein.

A "flowable" product as referred to herein is a liquid, semi-liquid, powdered or particulate product which when poured with or without the application of pressure flows out of a container even if the product does not flow out in a continuous stream. The term does not include products which are in one piece (e.g. have a shaped solid form such as blocks, cubes etc) as these are not capable of flowing, nor, products which are eaten in a physical state which does not flow such as ice-cream.

The liquid or flowable edible compositions of the invention give good satiety effects, acceptable sensory properties (such as acceptable taste) and have a good balance of the level of whey protein and/or whey protein hydrolysate used and the percentage of calories in the product obtained from the total amount of protein in the composition. This combination is especially suitable for a meal replacement product.

body weight and/or body perception. There are also longer term advantages associated with helping in the prevention of diseases related to being overweight.

Except in the operating and comparative examples, or where otherwise explicitly indicated, all numbers in this description indicating amounts of material or conditions of reaction, physical properties of materials and/or use are to be understood as modified by the word "about". All amounts are as percentages by weight unless otherwise stated. For the edible compositions, all percentages are by weight based on the total weight of the composition unless otherwise stated.

The term "comprising" is meant not to be limiting to any subsequently stated elements but rather to encompass non-specified elements of major or minor functional importance. In other words the listed steps, elements or options need not be exhaustive. Whenever the words "including" or "having" are used, these terms are meant to be equivalent to "comprising" as defined above.

DETAILED DESCRIPTION

Satiety peptides

Cholecystokinin(s) and "CCK" as used herein include all peptides of the CCK family, including (but not limited to); CCK-4, CCK-8, CCK-22, CCK-23, CCK-24, CCH-25, CCK-36, CCK-27, CCK-28, CCK-29, CCK-30, CCK-31, CCK-32, CCK-33, CCK-39, CCK-58.

Glucagon-like-peptides (GLP) and "GLP" as used herein include all peptides of the GLP family including (but not limited to); GLP-1 and GLP-2. GLP-1 has been found to be especially of interest.

cellular release of CCK and GLP in the body is stimulated resulting in the satiety effect.

This cellular release can also be measured *in vivo*, for example, by measuring the increase or appearance of CCK and GLP levels in the blood of that subject after consumption of the WP and/or WPH or an edible composition comprising it. Suitable techniques for measuring the CCK and GLP levels in the blood are well known in the art and do not need to be further described here.

The WP and/or WPH of the invention show cellular release of CCK and GLP-1 in the *in vitro* cellular release test of examples 1 and 2, particularly, when used at a concentration of at least 5mg/ml.

Without wishing to be bound by theory, it is believed that the WP/WPH of the invention may provide enhanced satiety effects by at least one of the following mechanisms:

1) by triggering the release of CCK from the duodenal and jejunum mucosal (I) cells and by triggering the release of GLP-1 from mucosal L cells in the distal ileum and colon from processing of major proglucagon fragment by prohormone convertase PCI/3.
2) CCK-like peptides in the WP/WPH may activate CCK-A receptors on the gastric pylorus causing contraction resulting in gastric distension. Stomach distension activates receptors on the afferent gastric vagus nerve, which then transmits signals via the nucleus tractus solitarius (NTS) to the satiety centre of the hypothalamus.
3) CCK-like peptides in the WP/WPH may bind to receptors present in the area postema adjacent to the NTS at the base of the fourth ventricle. The blood brain barrier overlying

It is especially preferred that the WPH comprises hydrolysates of β-lactoglobulin or α-lactalbumin, most preferably mixtures thereof. The weight ratio of the β-lactoglobulin or α-lactalbumin hydrolysates in the mixture is preferably in the range of from 5:1 to 1:5, more preferably 4:1 to 1:4, such as 3.5:1 to 1:2.

One particular WPH which may be used comprises from 5 to 20% by weight of aspartic acid, 10 to 25% by weight of leucine, 5 to 20% by weight of lysine and 10 to 32 % by weight of glutamic acids.

The WPH may have a degree of hydrolysis in the range of up to 20%, preferably of from 1 to 15%, more preferably of from 2 to 10%, such as 5 to 9%. The degree of hydrolysis is determined by OPA methodology (Lee KS, Drescher DG., Fluorometric amino-acid analysis with o-phthaldialdehyde (OPA), Int. J. Biochem. 1978; 9(7): 457-467).

The WP and WPH preferably have a weight average molecular weight in the range of from about 1000 Dalton to 12000 Dalton, preferably of from 2000 Dalton to 8000 Dalton. It is preferred that 4 to 40% by weight, more preferably 10 to 30% of the WPH has a weight average molecular weight in the rage of from 2000 to 5000 Daltons and/or 1 to 30% by weight, more preferably 2 to 20 % of the WPH has a weight average molecular weight in the range of from 5000 to 10000 Daltons.

The WP and WPH preferably have a pH in the range of from 6 to 9 at 20°C in a 10 mg/ml solution in de-ionised water, more preferably of from 6.5 to 8.

administering to a human or animal an effective amount of the WP and/or WPH of the invention.

The total effective amount of WP and/or WPH administered according to the method may vary according to the needs of the person to whom it is administered. Typically total amounts of from 0.1g to 150g will be administered, preferably 1g to 80g, more preferably 5g to 50g per day. The effective daily amount may be administered by a single dose or by multiple doses.

The WP and/or WPH may be administered to the animal or human in any suitable form, for example as a capsule, tablet, solution, or, preferably as part of an edible composition as described herein including bar products and liquid products such as ready-to-drink products.

The Edible Composition

The edible composition may be in the form of a nutritional composition or supplement (such as a tablet, powder, capsule or liquid product), a food composition (product) such as a meal replacement product or a beverage.

A nutritional composition or supplement as used herein refers to a composition or supplement which provides at least one biologically beneficial agent such as vitamins, minerals, trace elements, the WPH etc and which is intended to supplement the amount of such agents obtained through normal dietary intake.

A food composition according to the invention may be any food which can be formulated to comprise the WP and/or WPH and which also contains at least one of protein, fat, and/or carbohydrate. It is preferred that the food composition is one intended to be used in a weight loss or weight control plan.

convenient form. It is especially preferred that the meal replacement product is a ready to drink liquid, a liquid produced from a soluble powdered product, a soup, a dessert, a bar, a cereal based or pasta based or noodle based product, or, a soluble or dispersible powdered product.

The edible composition may be for example; a solid product, a powdered product, a tablet, a capsule, a liquid, a flowable, spoonable, pourable or spreadable product or a bar etc. The edible composition may be a powder which is mixed with a liquid, such as water or milk, to produce a liquid or slurry product (such as a meal replacement product).

The edible compositions comprise a total amount of from 0.1% to 80% by weight of the WP and/or WPH based on the weight of the composition, preferably 0.1 to 40 or 50 %wt, more preferably 0.5 or 1 to 30%wt, most preferably 2 or 5 to 20%wt. The edible compositions preferably comprise an amount of from 0.1 to 80% by weight, preferably 1 to 50%, of hydrolysates of β-lactoglobulin, α-lactalbumin or mixtures thereof based on the weight of the composition.

According to one embodiment of the invention, the edible compositions may comprise less than 20 g in total per serving, or per product where the product is used as a single serving, of the WP and/or WPH whether or not the above-mentioned amounts are used.

If the edible composition is a liquid or flowable composition, such as liquid meal replacement product or a soup, then the total amount of WP and/or WPH will preferably be in the range of from 0.1 to 40 or 50% by weight, more preferably 0.5 or 1 to 30%wt, most preferably 2 to 20%wt based on the total weight of the composition.

The edible composition will typically comprise protein in addition to the WP and/or WPH. The total amount of protein in the composition is preferably an amount of from 0.1 to 30 or 40% by weight of the edible composition. It is preferred that the compositions comprise 0.5 to 25%wt of total protein, preferably 1 to 20 %wt. In the liquid or flowable compositions the protein present provides up to 50% of the total calories of the edible composition, more preferably between 20 % and 50%, most preferably between 25% and 50%. For the other types of edible compositions, these amounts are preferred but are not essential.

The edible composition may comprise edible fats, preferably in an amount of up to 60 or 70% by weight based on the weight of the composition, more preferably from 0.5 to 30 or 35%wt, most preferably from 0.75 to 10 or 20% fat. Any suitable fat may be used with vegetable fats being especially preferred for example, vegetable fats, plant oils, nut oils, seed oils, or mixtures thereof. Saturated or unsaturated (mono-unsaturated and poly-unsaturated) fats may be used.

The edible compositions may also comprise one or more carbohydrates, preferably in an amount of from 1 to 95% by weight based on the weight of the composition, more preferably 5 to 70%wt, most preferably 10 to 60%wt, such as 15 to 50%wt. Any suitable carbohydrate may be used, for example sucrose, lactose, glucose, fructose, corn syrup, maltodextrins, starch, modified starch or mixtures thereof.

The edible composition may also comprise dietary fibres, for example in an amount of from 0.1 to 40 or 50% by weight based on the weight of the composition, preferably 0.5 to 20%wt.

The edible composition may also comprise 0.1 to 15% by weight of edible salts based on the weight of the composition, preferably 3 to 8%wt. Any edible salts may be used, for example, sodium chloride, potassium chloride, alkali metal or alkaline earth metal salts of citric acid, lactic acid, benzoic acid, ascorbic acid, or, mixtures thereof. Calcium salts may also be used such as calcium chloride and calcium caseinate.

The edible composition may comprise one or more cholesterol lowering agents in conventional amounts. Any suitable, known, cholesterol lowering agent may be used, for example isoflavones, phytosterols, soy bean extracts, fish oil extracts, tea leaf extracts.

The edible composition may comprise up to 10 or 20% by weight, based on the weight of the composition, of minor ingredients selected from added vitamins, added minerals, herbs, spices, flavourings, aromas, antioxidants, colourants, preservatives or mixtures thereof. Preferably the compositions comprise of from 0.5 to 15% by weight, more preferably 2 to 10% of these ingredients. It is especially preferred that the compositions comprise added vitamins and minerals. These may be added by the use of vitamin premixes, mineral premixes and mixtures thereof. Alternatively the vitamins and/or minerals may be added individually. These added vitamins and/or minerals are preferably selected from at least one of vitamins A, B1, B2, B3, B5, B6, B12, biotin, C, D, E, H, K and calcium, magnesium, potassium, zinc and iron. Iodine, manganese, molybdenum, phosphorus, selenium and chromium may also be included.

The amounts of protein, fat, carbohydrate and other ingredients in the edible composition will vary according to the product

trace elements. Fibres, although not absorbed by the body, are considered herein as nutrients. Water, although it provides a benefit to the body, is not considered as a nutrient.

The consumption of a composition comprising the WP and/or WPH according to the invention may occur as a part of a dietary plan, such as those intended to reduce or control body weight. For example, a subject following that plan may be better able to reduce, control or maintain their body weight, e.g. by following the dietary plan for a longer period of time and/or adhering more closely to the plan as they feel less temptation to snack or over-eat. The term "dietary plan" as used herein includes those for controlling body weight and those followed for medical reasons.

Another advantage of the present invention is that it provides methods and compositions to treat obesity or alter gastric transit and nutrient uptake in the body, which compositions can be simply eaten rather than needing to be injected as occurs with some hormones used in the treatment of obesity.

The invention is further described by way of the following examples which are to be understood as not limiting. Further examples within the scope of the invention will be apparent to the person skilled in the art.

EXAMPLES

Examples 1 and 2: Stimulated release of GLP 1 and CCK in cultured GLUTag cells

1. Materials

a) Whey Protein Hydrolysate:

cells/well) and the plates were stored under the same incubation conditions as described above. After 3 days storage the cells were washed twice with DMEM containing 0.5% (vol/vol) FBS and then, to four series (A to D) of 3 wells, different amounts of Biozate 1 were added as detailed below. Thus, each series was prepared in triplicate. A control sample which did not have any added Biozate 1 was also prepared in triplicate.

Series A - 0.5 mg/ml Biozate 1
Series B - 3 mg/ml Biozate 1
Series C - 5 mg/ml Biozate 1
Series D - 10 mg/ml Biozate 1

The plates were incubated as detailed above and after incubation for 1 hour an aliquot was taken from each plate to measure CCK release. A further aliquot was taken from each plate after 2 hours incubation to measure GLP-1 release. The aliquots were treated as detailed below before being tested to determine CCK or GLP-1 release.

The aliquots were collected and 50μg/ml phenylmethanesulfonyl fluoride (PMSF) was added thereto. The aliquots were frozen at -80°C for subsequent analysis for CCK and GLP-1 secretion. The aliquots were defrosted and centrifuged (5000g) to remove cell debris. The CCK and GLP-1 release from the GLUTaq cells was then tested.

CCK release was measured using a commercial enzyme immunoassay kit (from Phoenix Pharmaceuticals, Belmont, California, USA) which measures CCK 26-33 non-sulfated and sulfated. According to the test kit specifications, the intra-assay variation is <5% and the inter-assay variation is <14%.

EXAMPLE 3 - meal replacement bar product

A meal replacement bar product comprising WPH may be prepared according to the formulation below.

Ingredient	Percentage by weight
Honey	16.0
Sucrose	10.0
Biozate 1 (WPH)	13.0
Whey protein*1	13.0
Chopped dried fruit and nuts	10.0
Soy flour	5.0
Peanut butter	5.0
Maltodextrin	4.0
Oats	6.0
Bran fibre	2.0
Flavourings	2.0
Vitamin / mineral premix	2.0
Chocolate flavoured coating	to 100 %wt

*1 not according to the present invention.

The bar is made by thoroughly mixing together the honey and maltodextrin with the peanut butter. The remaining ingredients except the chocolate flavoured coating are added and the mixture is further mixed and formed into a bar shape. To coat it the bar is passed through a curtain of molten chocolate flavoured coating. The bar is allowed to cool to solidify the coating.

The edible composition shows good satiety effects compared to the equivalent composition wherein the whey protein hydrolysate is replaced by the same amount of cow's milk protein.

Ingredient	Percentage by weight
Maltodextrin	39.4
Tea powder	9.0
Aspartame	2.5
Peach flavour	3.6
N&A apricot flavour	1.2
Citric acid	9.0
Magnesium oxide	0.2
Biozate 1	10.0
Vitamin premix	0.3
Calcium lactate	23.2
Water	to 100 %wt

The product shows good satiety effects (may be consumed as a diluted product) compared to the equivalent composition wherein the whey protein hydrolysate is replaced by the same amount of cow's milk protein.

In examples 3 to 5 the whey protein hydrolysate may be replaced by the non-hydrolysed whey protein according to the present invention.

used in a total amount of from 0.1% to 80% by weight based on the weight of the composition.

7. The use according to any one of the preceding claims, wherein the edible composition is a food composition used in a weight loss or weight control plan.

8. The use according to any one of the preceding claims, wherein the edible composition meal replacement product.

9. The use according to claim 8, wherein the meal replacement product is a ready-to-drink liquid, a liquid produced from a soluble powdered product, a soup, a dessert, a bar, a cereal based or pasta based or noodle based product, or, a soluble powdered product.

10. A method for inducing satiety in a human or animal, the method comprising the step of administering to a human or animal by means of an edible composition, an effective amount of a whey protein and/or whey protein hydrolysate which is capable of inducing the cellular release of glucagon-like peptides and cholecystokinins.

11. A method for improving or controlling perception of body image, and/or controlling body weight, and/or controlling calorie intake and/or helping adherence to a dietary plan, the method comprising the step of administering to a human or animal by means of an edible composition, an effective amount of a whey protein and/or whey protein hydrolysate which is capable of inducing the cellular release of glucagon-like peptides and cholecystokinins.

17. The edible composition according to any one of claims 13 to 16, wherein the composition is used in a weight loss or weight control plan.

18. The edible composition according to claim 17, wherein the composition is a meal replacement product.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/305 A23L1/29 A23L2/66 A23J3/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 207 638 B1 (PORTMAN ROBERT) 27 March 2001 (2001-03-27) cited in the application column 7, line 37-53; claim 1 column 9, line 18-59 ---	1,2,6-12
X	WO 99 49741 A (NESTLE SA ;BOZA JULIO (CH); BALLEVRE OLIVIER (CH); FINOT PAUL ANDR) 7 October 1999 (1999-10-07) cited in the application page 4, paragraph 4; examples page 6, paragraph 4 --- -/--	13-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/06212

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 6207638	B1	27-03-2001	AU	4176201 A	03-09-2001
			CA	2400312 A1	30-08-2001
			EP	1259112 A1	27-11-2002
			JP	2003523368 T	05-08-2003
			WO	0162086 A1	30-08-2001
			US	2003008810 A1	09-01-2003
			US	6468962 B1	22-10-2002
			US	2001021694 A1	13-09-2001
			US	2002019334 A1	14-02-2002
WO 9949741	A	07-10-1999	AT	237957 T	15-05-2003
			AU	3142099 A	18-10-1999
			BR	9909234 A	28-11-2000
			CA	2326148 A1	07-10-1999
			CN	1303238 T	11-07-2001
			DE	69907170 D1	28-05-2003
			DK	1065947 T3	14-07-2003
			WO	9949741 A1	07-10-1999
			EP	1065947 A1	10-01-2001
US 2002044988	A1	18-04-2002	AU	9177701 A	04-03-2002
			AU	9548801 A	04-03-2002
			BR	0113367 A	29-07-2003
			BR	0113390 A	29-07-2003
			CA	2418285 A1	28-02-2002
			CA	2419026 A1	28-02-2002
			WO	0215719 A2	28-02-2002
			WO	0215720 A2	28-02-2002
			EP	1313378 A2	28-05-2003
			EP	1313376 A2	28-05-2003
			HU	0301475 A2	28-08-2003
			HU	0301586 A2	28-08-2003
			US	2002044957 A1	18-04-2002
EP 1034704	A	13-09-2000	EP	1034704 A1	13-09-2000
			AU	3807700 A	04-10-2000
			BR	0008916 A	15-01-2002
			CA	2364031 A1	21-09-2000
			CN	1343095 T	03-04-2002
			CZ	20013288 A3	13-02-2002
			WO	0054603 A1	21-09-2000
			EP	1161152 A1	12-12-2001
			HU	0200292 A2	29-05-2002
			JP	2002538797 T	19-11-2002
			NO	20014297 A	05-11-2001
			NZ	513918 A	29-08-2003
			PL	350227 A1	18-11-2002
			SK	12822001 A3	07-01-2002
			TR	200102601 T2	21-01-2002
			ZA	200106744 A	25-11-2002
WO 0143563	A	21-06-2001	AU	2167901 A	25-06-2001
			WO	0143563 A1	21-06-2001
EP 1201137	A	02-05-2002	EP	1201137 A1	02-05-2002
			AU	8156701 A	02-05-2002
			CA	2359606 A1	24-04-2002
			JP	2003033197 A	04-02-2003